Dietary Reference Intakes for vitamin D: justification for a review of the 1997 values[1–3]

Elizabeth A Yetley, Danielle Brulé, Margaret C Cheney, Cindy D Davis, Krista A Esslinger, Peter WF Fischer, Karl E Friedl, Linda S Greene-Finestone, Patricia M Guenther, David M Klurfeld, Mary R L'Abbe, Kathryn Y McMurry, Pamela E Starke-Reed, and Paula R Trumbo

ABSTRACT

Recent Institute of Medicine (IOM) reviews of the process for deriving Dietary Reference Intakes (DRIs) suggest that determining the need for a new nutrient review should be evaluated against criteria set a priori. After selecting the criterion of significant new and relevant research, a working group of US and Canadian government scientists used results from a systematic review and 2 conferences on vitamin D and health to evaluate whether significant new and relevant scientific evidence had become available since the 1997 IOM publication of the DRIs for vitamin D. This working group concluded that there appears to be new research meeting the criteria for 4 key DRI questions. The new research is of larger quantity and quality for the elderly than for other groups, but overall *1*) adds to the bone-related and status evidence available to the 1997 DRI Committee for several of the life-stage groups, *2*) identifies new outcomes with respect to risk of falls and performance measures in the elderly and potential adverse effects, and *3*) provides additional information on dose-response relations between intakes and circulating 25-hydroxyvitamin D concentrations and between 25-hydroxyvitamin D concentrations and several health outcomes (ie, bone-related outcomes for all ages and risk of falls and performance measures in older adults). Members of the working group concluded that significant new and relevant research was available for reviewing the existing DRIs for vitamin D while leaving the decision of whether the new research will result in changes to the current DRIs to a future IOM-convened DRI committee. *Am J Clin Nutr* 2009;89:719–27.

INTRODUCTION

In the past, when the Institute of Medicine (IOM) revised the Recommended Dietary Allowances, when Health Canada revised the Recommended Nutrient Intakes (RNIs), and more recently when the IOM derived the Dietary Reference Intakes (DRIs), a review of all the nutrients and related substances with reference values was conducted regardless of whether relevant new research had become available. It is anticipated that future DRI reviews will not continue to comprehensively review all nutrients on a regular basis, but rather will focus on a single or a small number of related nutrients (eg, vitamin D and calcium). Determining when a nutrient review meets so-called trigger criteria therefore becomes an important threshold to consider before initiating a review (1, 2).

New and relevant research on the biological knowledge about the nutrient is one threshold that has been suggested for prioritizing new reviews (1, 2). The quality and number of new studies will influence this prioritization. Research recommendations in the 1997 DRI review (3) and an IOM-sponsored workshop (4) identified the need for research to evaluate the intake requirements for vitamin D as related to optimal circulating 25-hydroxyvitamin D [25(OH)D] concentrations across life stage and race-ethnicity groups of US and Canadian populations, taking into account variabilities in ultraviolet B radiation (UVB) exposures. The 3 steps for defining optimal vitamin D intakes were described as *1*) identifying the biological actions affected by vitamin D, *2*) determining the concentration of 25(OH)D needed to optimize function for those biological ac-

[1] From the Agricultural Research Service (DMK) and the Center for Nutrition Policy and Promotion (PMG), US Department of Agriculture, Washington, DC; the US Army Medical Research and Material Command, Ft Detrick, MD (KEF); the Bureau of Nutritional Sciences, Food Directorate (PWFF and MRL), and the Office of Nutrition Policy and Promotion, Health Canada, Ottawa, Canada (DB, MCC, and KAE); the Center for Food Safety and Applied Nutrition, US Food and Drug Administration, College Park, MD (PRT); the Division of Nutrition Research Coordination (PES-R), National Cancer Institute (CDD), and Office of Dietary Supplements (EAY), National Institutes of Health, Bethesda, MD; the Office of Disease Prevention and Health Promotion, US Department of Health and Human Services, Washington, DC (KYM); and the Public Health Agency of Canada, Ottawa, Canada (LSG-F).

[2] The authors are responsible for the content of this article. The perspectives contained herein may not represent official opinions or positions of the United States and Canadian government organizations with which the authors are affiliated.

[3] Address correspondence and reprint requests to EA Yetley, Office of Dietary Supplements, National Institutes of Health, 6100 Executive Boulevard, Room 3B01, Bethesda, MD 20892-7517. E-mail: beth@yetley.com.

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tions, and *3*) defining the relation between intakes and circulating 25(OH)D (4). It was also noted that progress has been made in studying vitamin D safety.

This article describes the approach and rationale used by a working group of US and Canadian government scientists in deciding whether a review of the 1997 vitamin D DRIs is currently warranted. In the spirit of recent discussions on the need for increased transparency in DRI-related decisions (1, 2), potential government sponsors of a future vitamin D DRI revision are sharing their rationale as to whether funding of a review of the DRIs for vitamin D met reasonable trigger criteria. This article does not provide any conclusions on the appropriateness of current DRI reference values or recommendations for safe and adequate vitamin D intakes, because this is the independent responsibility of a future DRI Committee.

FRAMEWORK FOR THE JUSTIFICATION

At the beginning of this process, the working group determined what the threshold criterion should be for evaluating whether a review of vitamin D is justified. The criterion selected was that significant new and relevant research had become available after the 1997 DRI committee completed their deliberations. This criterion was selected because it was identified in recent discussions of potential trigger criteria for new DRI reviews (1, 2). However, whether there is significant new evidence supportive of a need to review existing vitamin D intake reference values is a point of considerable controversy. For example, some scientists and professional groups have suggested that new evidence demonstrates the need to update the current DRIs by increasing, sometimes significantly, the reference values for both adequacy and safety (5–9). Conversely, an evaluation by an expert panel convened by the UK government of the scientific evidence available within a similar time frame found in 2007 that the available evidence lacked a definitive basis on which to revise their 1991 vitamin D reference intake value of 10 μg/d (400 IU) for persons aged ≥65 y (10). Not only do these concurrently developed intake guidelines (5–10) indicate wide differences, they also differ from the 1997 DRI values for vitamin D (3) (**Table 1**). While recognizing the inconsistencies among government-supported consensus guidelines set 10 y apart (3 compared with 10) and the widely varying perspectives among some scientists and professional groups on whether the 1997 vitamin D DRI values need to be revised (5–10), the working group felt that advocacy positions of some scientists and groups or cited differences among consensus guidelines were not a sufficient basis on which to inform pending funding decisions for a new vitamin D review. Rather, the availability of significant new and relevant research was deemed a necessary criterion for informing the decision of when a review of the 1997 DRIs is warranted. This criterion minimizes the likelihood that public pressures alone will drive the DRI process. It also provides assurance that a new Committee will have new research to inform their deliberations.

The working group did not evaluate whether or how the availability of new research might result in changes to the current DRIs. A decision that a review is warranted (ie, triggered) is a funding decision. Therefore, it is important to maintain a separation between funding decisions and the necessary independence of the deliberative scientific process that is the hallmark of IOM-sponsored DRI Committees (11). Independence of DRI Committees is essential to ensuring the integrity of the scientific process by minimizing the likelihood that pressures from those outside the Committee process will unduly influence the outcome of the scientific deliberations.

METHODS

To answer the question of whether significant new and relevant scientific research had become available since the 1997 DRI Committee likely completed its literature search, articles published since then were identified. (For the purposes of this document, the term "DRI Committee" is used to refer to the

TABLE 1
Vitamin D reference intakes from government-supported independent consensus panels and from several scientists and professional groups

	Government-supported independent consensus panels		
	Adequate Intake[1]	Dietary reference values[2]	Scientists and professional groups
	μg(IU)/d		*μg(IU)/d*
Adequate Intakes			
7 mo to 3 y	5 (200)	7 (280)	10 (400) (6)
4–18 y	5 (200)	—	10 (400) (6)
19–50 y	5 (200)	—	≥25 (1000) (7)
51–65 or 70 y	10 (400)	—	≥25 (1000) (7)
>65 or 70 y	15 (600)	10 (400)	≥25 (1000) (7)
Pregnant and lactating women	5 (200)	10 (400)	150 (6000) (8)
Upper Intakes			
All persons ≥1 y	50 (2000)[3]	25 (1000)[4]	250 (10,000) (9)

[1] Adequate Intakes, the Institute of Medicine's Dietary Reference Intake reference value, was used instead of a Recommended Dietary Allowance if sufficient scientific evidence was not available to calculate an Estimated Average Requirement (3).

[2] For vitamin D, set in 1991 and reiterated in 2007 by the Scientific Advisory Committee on Nutrition, United Kingdom (10). These values apply to healthy populations. Those at risk of inadequate sunlight exposure may require supplementation.

[3] Value is the Tolerable Upper Limit—the Institute of Medicine's Dietary Reference Intake value for the highest daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population (3).

[4] Value is the Safe Upper Intake—a population guidance level suggested by the UK's Expert Group on Vitamins and Minerals (10). This level would not be expected to cause adverse effects in the general population when consumed regularly over a long period.

collection of groups involved in the derivation of the 1997 DRIs for vitamin D, including the Standing Committee on the Scientific Evaluation of the Dietary Reference Intakes, the Panel on Calcium and Related Nutrients, and the Subcommittee on Upper Reference Levels of Nutrients.)

The relevance of new research was considered in relation to the 4 key questions as being central to DRI decision making.

Questions related to adequate vitamin D intakes for healthy populations:

1) What is the effect of circulating concentrations of 25(OH)D (an indicator of vitamin D adequacy) on health outcomes?
2) What is the effect of vitamin D intakes on circulating concentrations of 25(OH)D?
3) What is the effect of vitamin D intakes on health outcomes?

Question related to vitamin D intakes that are indicative of adverse effects for healthy populations:

4) What levels of vitamin D intakes are associated with adverse effects?

The "significance" of the new research was based on its scientific quality (eg, type of study and quality rating scores), the number of new studies, and whether the new study results appeared to expand the information available for the 1997 report with respect to key DRI decisions (eg, indicators of adequacy or hazard, dose-response curves, health outcomes, life-stage groups, and interpretability of relations between intakes, biomarkers, and outcomes). The working group was particularly interested in the availability of new randomized clinical trials (RCTs) of relatively high scientific quality because an IOM Committee had found that this type of research was most likely to avoid the dilemma of new research having no impact, either positive or negative, on the confidence level relative to the validity of a diet-health relation (12).

"New" research was defined as articles that were likely to have been unavailable to the 1997 DRI Committee. The Committee was established in April 1996 and its report was published in 1997 (3). We therefore classified publications after 1997 as "new" studies and publications before and during 1996 as "old" studies. We classified studies published during 1997 and cited in the 1997 DRI report as "old"; studies published in 1997 but not cited in the report as "new."

The working group identified new and relevant research by further analyzing results from a recent systematic review (13, 14). This review was conducted by the University of Ottawa Evidence-based Practice Center (EPC) and was designed to provide an independent, comprehensive, transparent, and reproducible review of 5 key questions related to relations between vitamin D exposures, circulating concentrations of 25(OH)D, and several health outcomes [eg, bone mineral density (BMD), fracture or fall risk, and potential harms]. The study populations included children, women of reproductive age, postmenopausal women, and elderly men. To minimize bias, study design was limited to RCTs whenever possible. The study quality of the RCTs was assessed by using the validated Jadad scale; a score of $\geq$3 (out of a possible 5) indicates studies of higher quality.

Because the key questions that guided the systematic review (13, 14) were very similar to the research needs identified for determining vitamin D intake requirements (3, 4) and because of the review's timeliness, comprehensiveness, and independence, this review provided a sound basis for identifying significant new and relevant research with respect to bone health—the primary basis for the 1997 DRIs. However, because the systematic review was not done to evaluate vitamin D DRIs but rather to set research agendas, the working group further analyzed the results to identify new compared with old studies with respect to the approximate time frame of the 1997 DRI Committee activities. The results presented below and in supplemental data (*see* Tables S1–S4 under "Supplemental data" in the online issue) reflect these additional analyses.

To identify new issues with possible relevance to interpreting research results within the DRI decision-making framework, the working group used summaries from 2 recent National Institutes of Health (NIH) conferences (15–18). (For the current article, conference summaries were relied on for the purpose of identifying key interpretive issues; however, the full range of the scientific perspectives presented at these conferences is available elsewhere; 19, 20). The relevant interpretive issues included an understanding of *1*) factors that may alter the dose-response relations that are at the core of DRI decisions, *2*) factors that affect the comparability of results across laboratories and over time, and *3*) issues to consider when evaluating safe and adequate intakes for the 14 life-stage groups for whom DRI values are established.

The NIH conference entitled "Vitamin D and Cancer: Current Dilemmas and Future Needs" was held in May 2007 (17, 18). The conference goals were to evaluate critically the scientific evidence related to vitamin D and cancer risk, to identify gaps in knowledge, and to determine the research needed to make science-based recommendations for vitamin D intake and exposure for cancer prevention. In September 2007, the NIH sponsored a conference entitled "Vitamin D and Health in the 21st Century: An Update" and a subsequent roundtable discussion among experts to evaluate the information from the systematic review and a range of scientific perspectives with respect to identifying research needs (15, 16).

SUMMARY OF NEW AND RELEVANT SCIENTIFIC RESEARCH

Based on the additional analyses of information from the systematic review (13, 14), the availability of significant new and relevant research relative to each of the 4 DRI questions is summarized below.

What is the effect of circulating concentrations of 25(OH)D (an indicator of vitamin D adequacy) on health outcomes?

As shown in **Table 2**, the systematic review (13, 14) identified a total of 79 RCTs and observational studies with relevance to the effect of 25(OH)D concentrations on bone health outcomes for several life-stage groups and on falls and other performance measures in older populations. Fifty-seven (72%) of these studies met the definition of "new" and therefore would not likely have been available for the 1997 DRI report. The new references included 10 citations for RCTs, which added significantly to the 7 RCTs that would have been available to the 1997 DRI Committee. However, all but 2 of the new RCTs were conducted with postmenopausal women and older men. For the new RCTs, all but one received a Jadad score of $\geq$3, which suggested that the majority were of high quality (13, 14). The poorest quality rating was for the RCT that examined rickets in infants and young children.

TABLE 2
Effect of circulating 25-hydroxyvitamin D concentrations on bone health outcomes, falls, and performance measures[1]

Group	Health effect	Study type and ratio of new to total studies[2]	Quality of new RCTs[3]
Infants and young children (adapted from reference 13, Table 1, pp 35–40)	Rickets	RCT, 1:1 Before-after, 0:4 Case control, 6:8 Total, 7:13	1
Infants (adapted from reference 13, Table 2, pp 44–50)	Bone health	RCT, 0:3 Case-control, 3:4 Total, 3:7	
Older children and adolescents (adapted from reference 13, Table 3, pp 55–59)	Bone health	RCT, 1:2 Cohort, 3:3 Case control, 1:1 Before-after, 1:1 Total, 6:7	4
Pregnant and lactating women (adapted from reference 13, Table 4, pp 64–67)	Bone health	Cohort, 3:3 Before-after, 1:1 Total, 4:4	—
Postmenopausal women and older men (adapted from reference 13, Table 6, pp 78–86)	Fractures	Cohort, 2:3 Case control, 8:13 Total, 10:16	—
Postmenopausal women and older men (adapted from reference 13, Table 7, pp 87–92)	Falls	RCT, 2:2 Cohort, 3:3 Case control, 1:1 Total, 6:6	3, 5
Postmenopausal women and older men (adapted from reference 13, Table 7, pp 87–92)	Performance measures[4]	RCT, 2:3 Cohort, 4:4 Total, 6:7	4, 5
Postmenopausal women and older men (adapted from reference 13, Table 8, pp 93–101)	BMD, BMC	RCT, 4:6 Cohort, 6:7 Case control, 5:6 Total, 15:19	4, 4, 4, 5

[1] Data adapted from Cranney et al, 2007 (13). RCT, randomized clinical trial; BMD, bone mineral density; BMC, bone mineral content. "Before-after" refers to studies in which vitamin D status was assessed before and after a vitamin D intervention. "Cohort" refers to observational studies with prospective cohort designs.

[2] "New" refers to references not likely to have been available to the 1997 Dietary Reference Intake Committee and included all studies published after 1997 and studies published during 1997 that were not cited in the master reference list for the 1997 Institute of Medicine's report "Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride" (3) and excluded studies published before and during 1996 and studies published during 1997 that were cited in the master reference list for the 1997 Institute of Medicine's report.

[3] The study quality for RCTs was assessed in the systematic review (13) by using the validated Jadad scale with a score of ≥ 3 (out of a possible 5) indicating studies of higher quality.

[4] Performance measures included parathyroid hormone, muscle strength, independence index, postural sway, reaction time, aggregate functional performance time, quadriceps strength, ability to rise from a chair, static balance, 8-ft (2.44 m) walk, timed supine-to-stand test, quadriceps strength, and walking speed.

Because of the paucity of RCTs for this question for most life-stage groups, the EPC made an exception to their focus on RCTs and included observational studies. Of 62 observational studies, 47 were new. Of these, 18 provided information for infants, older children and adolescents, and pregnant and lactating women.

Overall, for all cited studies (new and old), the studies in infants and young children reported results associated with mean or median 25(OH)D concentrations ranging from <30 to 50 nmol/L. For postmenopausal women and older men, 25(OH)D concentrations <30–80 nmol/L were associated with increased hip bone loss. For most groups, some studies provided information on the relations of 25(OH)D and parathyroid hormone (PTH) concentrations. Discordance between results from RCTs and observational studies were noted when relating 25(OH)D concentrations and BMD or bone mineral content in postmenopausal women and older men. Inconsistencies in evidence across all groups and health effects were noted as a challenge for determining threshold concentrations of 25(OH)D across groups and across health effects.

What is the effect of vitamin D intakes on circulating 25(OH)D concentrations?

In **Table 3**, the number of new RCTs identified by the systematic review (13, 14) for addressing the question of how vitamin D intakes relate to circulating 25(OH)D concentrations from dietary and supplemental sources for several life-stage groups is summarized. These results indicate that 52 of the 86 (60%) citations on the topic of intakes and 25(OH)D concentrations were new. For the trials in which intakes were provided by fortified foods, 10 of the 11 citations were new, and more than one-half had relatively high quality ratings. These studies

TABLE 3
Effect of vitamin D intakes and ultraviolet exposures on circulating 25-hydroxyvitamin D concentrations[1]

Group	Exposure source	Ratio of new to total RCTs[2]	Quality of new RCTs[3]
Adults (adapted from reference 13, Table 9, pp 108–110)	Fortified foods	10:11	1 (1 RCT)
			2 (3 RCTs)
			3 (2 RCTs)
			4 (4 RCTs)
Infants (adapted from reference 13, Table 12, pp 135–136)	Supplement	1:7	1 (1 RCT)
Pregnant or lactating women (adapted from reference 13, Table 12, pp 137–138)	Supplement	1:6	2 (1 RCT)
Children and adolescents (adapted from reference 13, Table 12, p 139)	Supplement	3:4	2 (1 RCT)
			3 (1 RCT)
			4 (1 RCT)
Premenopausal women and younger men (adapted from reference 13, Table 12, pp 140–142)	Supplement	7:9	1 (2 RCTs)
			2 (3 RCTs)
			3 (2 RCTs)
Mixture of younger and older adults, community dwelling (adapted from reference 13, Table 12, pp 142–143)	Supplement	3:4	1 (1 RCT)
			2 (2 RCTs)
Postmenopausal women and older men, community dwelling (adapted from reference 13, Table 12, pp 144–151)	Supplement	21:31	1 (2 RCTs)
			2 (6 RCTs)
			3 (7 RCTs)
			4 (3 RCTs)
			5 (3 RCTs)
Postmenopausal women and older men, institutionalized (adapted from reference 13, Table 12, pp 151–154)	Supplement	6:14	2 (3 RCTs)
			3 (3 RCTs)
Adults (adapted from reference 13, Table 11, pp 116–118)	Ultraviolet light	1:8	2 (1 RCT)

[1] Data adapted from Cranney et al, 2007 (13). RCT, randomized clinical trial.
[2] "New" refers to references not likely to have been available to the 1997 Dietary Reference Intake Committee and included all studies published after 1997 and studies published during 1997 that were not cited in the master reference list for the 1997 Institute of Medicine's report "Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride" (3) and excluded studies published before and during 1996 and studies published during 1997 that were cited in the master reference list for the 1997 Institute of Medicine's report.
[3] The study quality was assessed in the systematic review (13) by using the validated Jadad scale with a score of ≥3 (out of a possible 5) indicating studies of higher quality.

were conducted primarily in older adults, but several of them also included younger adults. For supplementation trials, 42 of the 75 citations met the criteria for new and almost one-half had quality ratings on the Jadad scale of ≥3. The largest number of new supplementation studies ($n = 27$) with the highest quality ratings was for older adults. For children and adolescents and for premenopausal women and younger men, 10 of 13 RCTs were new and 4 were of high quality. The lowest quality ratings and smallest numbers of new supplementation studies were for studies with infants and pregnant or lactating women. With the exception of these 2 groups, the ratio of new to total intake studies was relatively high.

Overall, the fortification studies in adults provided evidence on intakes ranging from 2.5 to 25 μg (100 to 1000 IU) vitamin D/d and resultant 25(OH)D concentrations from 15 to 40 nmol/L (13, 14). For supplementation trials, doses ranged from 2.5 to 25 μg (100 to 1000 IU)/d for infants, 12.5 to 100 μg (500 to 4000 IU)/d for pregnant and lactating women, 5 to 50 μg (200 to 2000 IU)/d for children and adolescents, 15 to 250 μg (600 to 10,000 IU)/d for premenopausal women and younger men, 10 to 45 μg (400 to 1800 IU)/d for mixed community-dwelling premenopausal and postmenopausal women or younger and older men, 2.5 to 250 μg (100 to 10,000 IU)/d for community-dwelling postmenopausal women and older men, and 5.75 to 225 μg (230 to 9000 IU)/d for institutionalized postmenopausal women and older men. Trials varied in their use of vitamin D_2 or vitamin D_3. A few of the studies reported different effects of vitamin D_2 and vitamin D_3 on 25(OH)D concentrations. Dose-response relations between intakes and 25(OH)D concentrations were reported for several groups (eg, infants, children, and adolescents). For infants at northern latitudes, results suggested that 5 μg (200 IU) vitamin D_2/d may not be enough to prevent vitamin D deficiency. A quantitative analysis of supplementation trials suggested that vitamin D_3 doses ≥17.5 μg (700 IU)/d were significantly and consistently associated with lower PTH concentrations in vitamin D–deficient adult populations. A meta analysis of 17 trials in adults suggested that an increased intake of vitamin D_3 of 2.5 μg (100 IU)/d was associated with an increase in circulating concentration of 25(OH)D of 1 to 2 nmol/L.

The recent systematic review also addressed the question of the effect of ultraviolet exposures from both solar and artificial ultraviolet exposures as well as the impact of sunscreen use on circulating 25(OH)D concentrations (13). As shown in Table 3, the EPC identified 8 RCTs on this topic, although only 1 of these was new and it was of poor quality.

What is the effect of vitamin D intakes on health outcomes?

As shown in **Table 4**, the systematic review (13, 14) identified 43 RCTs that evaluated the effect of supplemental vitamin D intakes on BMD, fractures, and risk of falls in adults. All but one trial was conducted in postmenopausal women and older men.

TABLE 4
Effect of supplemental vitamin D intakes on health outcomes[1]

Group	Outcome	Ratio of new to total RCTs[2]	Quality of new RCTs[3]
Women of reproductive age, postmenopausal women and older men (adapted from reference 13, Table 13, pp 159–162)	BMD	12:17	≤2 (2 RCTs) ≥3 (10 RCTs)
Women of reproductive age, postmenopausal women and older men (adapted from reference 13, Table 15, p 172)	Fractures	10:13	2 (1 RCT) 3 (6 RCTs) 4 (2 RCTs) 5 (1 RCT)
Postmenopausal women and older men (adapted from reference 13, Table 16, pp 178–179)	Falls	11:13	3 (6 RCTs) 4 (2 RCTs) 5 (3 RCTs)

[1] Data adapted from Cranney et al, 2007 (13). RCT, randomized clinical trial; BMD, bone mineral density.
[2] "New" refers to references not likely to have been available to the 1997 Dietary Reference Intake Committee and included all studies published after 1997 and studies published during 1997 that were not cited in the master reference list for the 1997 Institute of Medicine's report "Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride" (3) and excluded studies published before and during 1996 and studies published during 1997 that were cited in the master reference list for the 1997 Institute of Medicine's report.
[3] The study quality was assessed in the systematic review (13) by using the validated Jadad scale with a score of ≥3 (out of a possible 5) indicating studies of higher quality.

Thirty-three of these trials (77%) were new. Most of the new RCTs had quality scores on the Jadad scale of ≥3.

Overall, by combining 7 trials that examined the question of vitamin D_3 and risk of fractures, a reduction in fracture risk was associated with 10–20 μg (400–800 IU)/d of vitamin D only when combining trials of institutionalized elderly, but this did not hold for noninstitutionalized older adults. Although most trials included co-interventions of vitamin D and calcium, a few trials compared combinations of vitamin D plus calcium against calcium only. These trials did not observe a benefit on BMD with the addition of vitamin D to the calcium intervention. A combined estimate from trials with higher final 25(OH)D concentrations suggested that 25(OH)D concentrations ≥74 nmol/L were consistent with a significant reduction in fractures.

What vitamin D intakes are associated with adverse effects?

The systematic review cited 22 RCTs in which some monitoring of adverse events was reported (**Table 5**) (13). Fifteen (68%) of these reports were new, 11 of which focused on older adults. Most of the new trials in older adults received a relatively high quality rating, whereas most of the studies in other life-stage groups were of relatively low quality.

Overall, most trials excluded subjects with renal insufficiency or hypercalcemia, were of small sample size, had short durations of vitamin D exposure, and low overall event rates. Most trials had treatment doses that exceeded current Adequate Intakes (AIs), and in a few cases, current Tolerable Upper Intake levels for vitamin D. Whereas most of these studies did not report any adverse effects of note, one "new" study reported an increased risk of renal stones with supplemental intakes of 10 μg (400 IU) vitamin D_3 and 1000 mg Ca/d in women aged 50–79 y.

SUMMARY OF NEW AND RELEVANT INTERPRETIVE ISSUES

The working group identified several interpretive issues relevant to vitamin D DRI decisions that were raised during the presentations and discussions of 2 recent conferences (15–20) and, to a limited degree, in the systematic review (13, 14). The working group focused on new issues that had not been discussed or were not fully developed in the 1997 DRI report. The conferences identified several factors affecting interpretation of the relations between intakes, indicators of adequacy or hazard, and functional outcomes (eg, baseline vitamin D and calcium status, race-ethnicity, oral contraceptive use, body mass index, and physical activity). They also identified problems of accuracy and excessive variability in measuring 25(OH)D and the vitamin D content of foods and supplements. While recognizing that 25(OH)D concentrations remain the best means of assessing vitamin D exposures, one conference report (16) noted that 25(OH)D concentrations are most useful at the extremes of the range for detecting deficiency and toxicity but are considerably less useful in the middle of the range. Moreover, the usefulness of 25(OH)D as an indicator of functional outcomes was found to be lacking or limited in many cases, with the possible exception of the elderly. Concerns about the interpretability of PTH concentrations in defining 25(OH)D cutoffs and assessing vitamin D status across life-stage groups were discussed. Different effects of vitamin D on calcium absorption, regulation, and requirements across life-stage and race-ethnicity groups were also noted. The conferences noted the difficulties in identifying the independent effects of vitamin D and calcium because most studies involved co-interventions with both nutrients. The systematic review (13) provided some information on the country and latitude for the 11 RCTs in which the effect of vitamin D delivered via fortified foods was examined. However, this information generally is not provided in research articles.

Interpretation of safety information is also integral to DRI decisions. Several conference presentations noted that animal data suggest that 25(OH)D concentrations must increase to >750 nmol/L to produce toxicity and some human studies suggest that intakes up to 250 μg (10,000 IU)/d have not been associated with adverse effects in humans. Others noted evidence suggesting that vitamin D might promote cancer risk in some individuals (eg, pancreatic cancer) (17, 18). It was also noted that the

TABLE 5
Reported safety outcomes[1]

Group	Safety outcome	Ratio of new to total RCTs[2]	Quality of new RCTs (quality score: no. of RCTs)[3]
Infants (adapted from reference 13, Table 18, p 191)	Hypercalcemia, hypercalciuria	1:2	≤2 (1 RCT)
Children (adapted from reference 13, Table 18, p 192)	Hypercalcemia, hypercalciuria, withdrawal because of adverse effects	1:1	≥3 (1 RCT)
Women predominantly of productive age ± middle-aged men (adapted from reference 13, Table 18, pp 192–193)	Hypercalcemia, hypercalciuria	2:2	≤2 (2 RCTs)
Predominantly postmenopausal women and/or elderly men (adapted from reference 13, Table 18, pp 193–204)	Serum calcium, hypercalcemia, hypercalciuria, kidney stones, mortality, gastrointestinal, ratio of urinary calcium to creatinine, 24-h urinary calcium, creatinine clearance, serum uric acid, high level of adverse effects, withdrawal because of adverse effects, osteomuscular effects, mortality, serum creatinine, total adverse events, renal insufficiency	11:17	≤2 (2 RCTs) ≥3 (9 RCTs)

[1] Data adapted from Cranney et al, 2007 (13). RCT, randomized clinical trial.
[2] "New" refers to references not likely to have been available to the 1997 Dietary Reference Intake Committee and included all studies published after 1997 and studies published during 1997 that were not cited in the master reference list for the 1997 Institute of Medicine's report "Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride" (3) and excluded studies published before and during 1996 and studies published during 1997 that were cited in the master reference list for the 1997 Institute of Medicine's report.
[3] The study quality was assessed in the systematic review (13) by using the validated Jadad scale with a score of ≥3 (out of a possible 5) indicating studies of higher quality.

available RCTs likely underestimated the true potential for risk for the following reasons: *1*) for ethical reasons, adverse outcomes are secondary outcomes; *2*) studies are of relatively short duration; *3*) adverse outcomes are not always adequately monitored or completely reported; and *4*) adverse outcomes generally lack adequate statistical power for detection (15–18). In addition, inclusion and exclusion criteria prevent persons at greatest risk from being study participants.

SUMMARY OF SIGNIFICANT NEW AND RELEVANT RESEARCH FOR A REVIEW OF THE 1997 DRIs FOR VITAMIN D

Whether there is significant new and relevant research sufficient to trigger a review of the 1997 vitamin D DRIs was addressed by the working group within the context of the 4 key DRI-related questions identified at the beginning of this article. These questions address relations between intakes, indicators of adequacy, and functional outcomes (both beneficial and adverse). Because DRI values were derived for 10 age and sex groups and for 2 age groups each for pregnant and lactating woman, these questions are applied to all 14 life-stage groups (3). Other vulnerable groups requiring special consideration within the DRI context were also discussed.

How and if the new research will affect revisions of the current vitamin DRIs are difficult to predict. A new DRI Committee will have access to articles published after the systematic review (13) was completed. They are likely to augment the identified studies with other studies not selected for the review. Moreover, they may add nutrition-related quality ratings to the study design–related quality ratings used in the systematic review when weighing the usefulness of individual studies. The new Committee will also need to decide how best to deal with the many uncertainties identified in the available literature and conferences.

The complexities of the DRI decision-making process mean that the availability of significant new and relevant research could affect the status of current DRI reference values in several ways. It could result in increased or decreased confidence in the current values (12), which would result in a reconfirmation of the values with updated descriptions of associated uncertainties. Alternatively, new evidence could result in revised DRIs for one or more life-stage group. These changes could reflect *1*) the selection of different indicators of adequacy or hazard and/or functional outcomes; *2*) changes in actual reference values because of different indicators or outcomes or because of the refinement of the dose-response relations between intakes, indicators, and outcomes; *3*) changes in the type of reference values provided (eg, an Estimated Average Requirement rather than an AI); or *4*) changes in how evidence from the studied groups is generalized to those groups for which evidence is limited or lacking. Finally, "no decision" is generally not an option for DRI Committees (1, 2). Given the many policy and health care applications for DRI reference values for nutrients and other substances of proven health benefit, the DRI process provides for the use of scientific judgment in dealing with the inevitable uncertainties in the available evidence.

DRIs for adequate intakes

The 1997 DRI Committee selected circulating concentrations of 25(OH)D as the best indicator for determining the adequacy of vitamin D intakes (3). There appears to be continued scientific agreement that circulating 25(OH)D concentrations are currently the best available indicator of total vitamin D exposures (15–18). However, in addition to the confounding effects of ultraviolet exposure and endogenous synthesis discussed in the 1997 DRI report, several interpretive issues not discussed or fully developed in this report provide new information on

confounders that need to be taken into consideration when interpreting this biomarker (eg, assay differences, adiposity, physical activity, baseline vitamin D and calcium status, oral contraceptive use, and race-ethnicity).

The 1997 DRI Committee identified several functional outcomes for deriving AIs. The Committee used linear growth and bone mass for infants and the absence of overt symptoms of vitamin D deficiency for children as the primary outcomes (3). For adults, calcium balance, PTH concentrations, and measures of bone health were used as outcome measures. Because the systematic review (13, 14) and one of the conferences (15, 16) focused primarily on bone health, their results are directly relevant to updating the 1997 report. The systematic review identified 57 new RCTs and 47 observational studies relating 25(OH)D concentrations to bone-related health outcomes, 52 new RCTs relating vitamin D intakes to 25(OH)D concentrations, and 33 new RCTs directly relating intakes to health outcomes. Many of these studies were of high scientific quality. The new research identified 2 new health outcomes that were not considered by the 1997 DRI Committee—falls and performance measures in older adults. However, most of the new studies and the highest quality studies were conducted in postmenopausal women and older men, thereby adding significantly to the available evidence for this group while contributing limited new evidence, often of poor quality, for other groups. The 1997 DRI Committee used PTH concentrations to aid in interpreting 25(OH)D concentrations, and a number of studies in the systematic review provided information on PTH/25(OH)D relations in the studied groups. New information from the NIH conference discussed caution in interpreting PTH/25(OH)D relations across life-stage groups.

The 1997 DRI Committee used a 25(OH)D cutoff of $\geq$27.5 nmol/L (11 ng/mL) for children and $>$30 nmol/L (12 ng/mL) for adults for assessing adequacy (3). The systematic review cited results from studies showing 25(OH)D concentrations in infants and young children ranging from $<$30 to 50 nmol/L (13). For older adults, 25(OH)D concentrations $<$30–80 nmol/L were associated with increased hip bone loss. Overall, the evidence provides information on mean or median 25(OH)D concentrations that extended above and, in some cases below, the cutoffs used by the 1997 DRI Committee. Information from the systematic review (13) and conferences (15–18) cautioned that different assays resulted in differences in 25(OH)D concentrations, thereby making comparisons across research sites and over time and the identification of threshold concentrations difficult.

The DRI Committee identified AIs of 5 μg (200 IU)/d for children $>$6 mo of age through adults up to 50 y and for pregnant and lactating women (3). For adults 51–70 y of age, an AI of 10 μg (400 IU)/d was established. The corresponding value for adults $>$70 y of age was 15 μg (600 IU)/d. (The AI was used instead of the more familiar Recommended Dietary Allowance, derived from the Estimated Average Requirement, because of uncertainties in sun exposure and body stores of study participants and potential errors in food composition values.) Overall, the available studies provided information on intakes ranging from 2.5 to 50 μg (100 to 2000 IU)/d in infants and children and from 2.5 to 250 μg (100 to 10,000 IU)/d in adults. Thus, the new information in combination with earlier research provides a basis for more complete information on dose-response relations.

The systematic review summarized 8 RCTs relating UVB exposures to 25(OH)D concentrations. Because this topic was not systematically reviewed by the 1997 Committee but was a source of considerable uncertainty, the availability of this summary in the systematic review, even if most of the identified publications were "old," could be useful to a future DRI Committee.

The 1997 Committee, lacking sufficient evidence to directly estimate vitamin D requirements for young children, adult men, and lactating women, used results from older children, adult women, and nonlactating women, respectively, to derive AIs for these relatively unstudied groups. Whereas for most groups other than older adults, the actual number of new studies was small and often of poor quality, the number and quality of RCTs available at the time of the 1997 DRI report was also very limited. Thus, even for these groups, the new research could be informative to a future DRI Committee. Additionally, new information on groups for which special considerations may be warranted (eg, African Americans, obese individuals, and oral contraceptive users) was discussed (15, 16). Although it is unlikely that a DRI Committee would set a separate reference value for these and other subgroups, recent evaluations of the DRIs identified the need for more explanatory text in the reports with respect to user applications (1, 2). Consequently, descriptions of when and how DRIs for life-stage groups need to be adjusted when planning diets or assessing the vitamin D status of subgroups whose needs may vary somewhat from their broader life-stage group is anticipated as a likely type of revision to be included in future DRI updates. As such, this information is germane to the review of DRIs for US and Canadian populations.

DRIs for tolerable upper limits

The 1997 DRI report on vitamin D set Tolerable Upper Intake levels of 50 μg (2000 IU)/d for all persons $>$12 mo of age based on hypercalcemia (circulating calcium concentrations $>$2.75 nmol/L, or 11 mg/dL) (3). The systematic review identified 15 new RCTs, most of high scientific quality, that provided information on adverse event monitoring for studies conducted primarily with older adults. The new evidence provided evidence of few adverse effects. However, concerns were raised about potential previously unrecognized adverse effects of vitamin D, including an increased risk of renal stones in postmenopausal women with daily intakes of 10 μg (400 IU) vitamin D and 1000 mg Ca and an increased risk of pancreatic cancer. Conversely, conference presentations noted that animal data suggest that toxicities are unlikely to occur until 25(OH)D concentrations exceed 750 nmol/L and human intakes exceed 250 μg (10,000 IU)/d. It was recommended that the available safety information be interpreted with much caution (16).

CONCLUSIONS AND NEXT STEPS

On the basis of the results of the systematic review and of 2 conferences and related activities, the working group concluded that there appears to be significant new and relevant scientific research related to the 4 key DRI questions, particularly for elderly populations; however, significant uncertainties remain. New information on interpretive issues across the relevant life-stage groups was also identified.

Whereas there is currently considerable interest in other possible health benefits of adequate vitamin D intakes (eg, decreased risk of cancer, diabetes, and multiple sclerosis), the potential relation of these outcomes to vitamin D intakes and status is less well documented and understood than is the relation of vitamin D to bone health and the other outcome measures described above. The recent conference on vitamin D and cancer noted the urgent need for intervention trials to sort through apparent inconsistencies among observational studies as to whether vitamin D is beneficial, is adverse, or has no effect with respect to cancer risk across different cancer sites (17, 18). The other chronic diseases and possible health outcomes that have been associated with vitamin D in some studies have not yet been the subject of government-sponsored conferences or independent systematic reviews; however a new systematic review that will update the review used in this article is currently underway (21). It will cover a broad range of chronic disease and other health outcomes in addition to bone health.

Based on the conclusion that a new review is warranted, several government organizations have commissioned the IOM to sponsor a review of the 1997 DRIs for vitamin D and calcium. Calcium will be included in this review because of its known biological interactions with vitamin D, particularly for bone health outcomes, and because most RCTs used co-interventions of vitamin D and calcium supplementation making it impossible to separate the individual effects of either nutrient (13, 14). While the current evaluation used the preselected criterion of significant new and relevant evidence, it is anticipated that further discussions will be needed to more fully delineate the range of criteria and procedures for deciding if and when other DRI nutrient reviews are warranted.

The authors' responsibilities were as follows—EAY: responsible for the approach used, the analysis, and the drafting of the article. All other authors served as members of the Vitamin D DRI Working Group on behalf of their respective government organizations. They provided input on the basic approach and criteria to be applied as well as critical review and comment throughout the development of the article. The authors had no financial conflicts of interest. The primary author (EAY) was a reviewer for the systematic review (13) used in this article. Her review was conducted under procedures of the Agency for Healthcare Research and Quality (AHRQ) that ensure the independence and integrity of the systematic review process by limiting interactions between persons associated with a sponsoring organization and the scientists conducting the systematic review to communications conducted through a designated AHRQ project officer. A review of a final draft by a member of the sponsoring organization was limited to comments related to factual errors, requests for clarification, and consistency with the original contract task order. Comments on the scientific content of the report were not provided by EAY because they would be inappropriate for a member of a sponsoring organization. In all cases, reviewer comments are advisory only and are not binding on the scientific authors of the final report. The online and bound copies of the systematic review clearly list the names of all reviewers of this report, including that of EAY. None of the authors had any conflicts of interest.

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